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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/852,922	05/10/2001	Toshihiro Kuroita	10089/14	5846

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EXAMINER	
HUTSON, RICHARD G	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 01/12/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/852,922	KUROITA ET AL.	
	Examiner	Art Unit	
	Richard G Hutson	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 October 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13,25-28 and 30-38* is/are pending in the application.

4a) Of the above claim(s) *13 and 31* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12,25-28,30 and 32-38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *6/03* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicants cancellation of claims 14-24 and 29 and amendment of claims 1, 4, and 5 and the addition of new claims 31-38, Paper of 6/26/2003, is acknowledged. Claims 1-13, 25-28 and 30-38 are still at issue and are present for examination.

Newly submitted claim 31 directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: claim 31 is drawn to a method for improving amplification efficiency and/or fidelity is related to the invention currently being prosecuted by

The invention of newly added claim 31 and Group I, currently being prosecuted, are related as process of making and product made. The inventions are distinct if either or both of the following can be shown: (1) that the process as claimed can be used to make other and materially different product or (2) that the product as claimed can be made by another and materially different process (MPEP § 806.05(f)). In the instant case the product can be made by a materially different process such as chemical synthesis.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claim 31 is withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Claims 13 and 31 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Information Disclosure Statement

Applicants filing of information disclosures, Paper of 6/26/2003, is acknowledged. Those references considered have been initialed.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 4-12, 25-28, 30 and 32 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The rejection of claims 4 and 5 was stated in the previous office action and repeated below for applicants convenience.

Claims 4-5 (Claims 6-12, 25-28 and 30 dependent on) previously recited the limitation " in the DIETLYH sequence (D: aspartic acid, I: isoleucine, E: glutamic acid, T: threonine,, L: leucine, Y: tyrosine, H: histidine) located at the 141-147-positions in the amino acid sequence of SEQ ID NO: 2," in the modified thermostable DNA polymerase according to claim 3. There was insufficient antecedent basis for this limitation in the claims from which these claims depend (i.e. claim 3). It is realized that the DIETLYH sequence is encompassed within those modified polymerases, comprising the $DX_1EX_2X_3X_4H$ sequence, claimed in claim 3, however the reference to the specific sequence "DIETLYH" is unclear.

Further as the only difference between claims 4 and 5, and claim 3, from which claims 4 and 5 depend, is the increased DNA extension rate (i.e. 30 or 40 vs. 20 bases/second) and increased thermostability (i.e. 40% or 60% vs. 10%), the recited physicochemical property (3) is interpreted as the amino acid sequence of the claimed modified thermostable DNA polymerase comprises SEQ ID NO: 2, wherein the histidine in the DIETLYH sequence at positions 141 to 147 of SEQ ID NO: 2, has been replaced with another amino acid.

In response to this rejection, applicants have amended claims 4 and 5 and state that the amendment was suggested by the examiner, thus overcoming the rejection. It is noted that the examiner made no suggestion as to how claims 4 and 5 should be amended. Further as was previously stated and repeated above, "the recited physicochemical property (3) **is/was interpreted** as the amino acid sequence of the claimed modified thermostable DNA polymerase comprises SEQ ID NO: 2, wherein the histidine in the DIETLYH sequence at positions 141 to 147 of SEQ ID NO: 2, has been replaced with another amino acid." Applicants have amended the recited physicochemical property (3) as: "amino acid sequence in the $DX_1EX_2X_3X_4H$ sequence (D: aspartic acid, X_1: isoleucine, E: glutamic acid, X_2 threonine, X_3: leucine, X_4: tyrosine, H: histidine) located at the 141-to 147- positions in the amino acid sequence of SEQ ID NO: 2, histidine (H) has been replaced by another amino acid." Based on applicants amendment it does not appear that the above previous interpretation of the physiochemical property (3) remains that the claimed modified thermostable DNA polymerase comprises SEQ ID NO: 2, wherein the histidine in the DIETLYH sequence

at positions 141 to 147 of SEQ ID NO: 2, has been replaced with another amino acid, but that rather the reference to SEQ ID NO: 2 is merely a reference to where the $DX_1EX_2X_3X_4H$ sequence can be found. Thus based on applicants amendment and the new interpretation of part (3), and applicants lack of any comment regarding the amendment or its interpretation, claims 4 and 5 are indefinite as being unclear and confusing.

Further applicants means of specifying residues X_1, X_2, X_3 and X_4 is unclear. It is suggested that applicants amend the claim to specifically state what amino acid residues $X_1EX_2X_3$ and X_4 are intended to be.

Claim 32 is indefinite in that the recitation "said DNA polymerase is a-like DNA polymerase" is confusing and unclear. Is it applicants intent that this recitation state "said DNA polymerase is an **alpha**-like DNA polymerase"?

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-12, 25-28, 30 and 32-38 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The rejection was stated in the previous office action as it applied to previous claims 1-3, 25-28 and 30. Claims 4-12 have been added to the rejection based on the above 112 second paragraph rejection. Applicants have amended claims 1, 4 and 5 and traverse the rejection as it applies to these newly amended claims. Claims 32-38 are included in this rejection for the same reasons previously stated for claims 1-3, 25-28 and 30.

Applicants traverse this rejection on the basis that it is known that the exonuclease I region of the thermostable DNA polymerase is highly conserved and embodiments of the present invention are directed to specific DNA polymerases having the $DX_1EX_2X_3X_4H$ sequence. Applicants further submit that the replacement of histidine (H) by another amino acid, especially aspartic acid, glutamic acid, tyrosine, alanine lysine and arginine, results in the claimed modified thermostable DNA polymerase with: (i) significantly reduced 3'-5' exonuclease activity; (ii) improved amplifying efficiency; or (iii) significantly improved 3'-5' exonuclease activity and/or fidelity on a DNA replication or amplification.

Applicants argument is not found persuasive because applicants have not provided a sufficient number of representative species having the $DX_1EX_2X_3X_4H$ sequence encompassed by these claims. There is no disclosure of any particular structure to function/activity relationship in the disclosed species, as is further elaborated by applicants argument that some of the claimed modified thermostable DNA polymerases have a reduced 3'-5' exonuclease activity while others have an increased 3'-5' exonuclease activity. The specification also fails to describe additional

representative species of these modified thermostable polymerases by any identifying structural characteristics or properties other than the minor structural limitation and activities recited in claims 1-3. Given this lack of additional representative species as encompassed by the claims, Applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise, and exact terms that a skilled artisan would recognize Applicants were in possession of the claimed invention. It is noted that claims 4-12 have been **included** in this rejection based on the above discussed (See 112 2nd paragraph rejection) interpretation of physicochemical property (3) of claims 4 and 5.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Claims 1-12, 25-28. 30 and 32-38 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a modified thermostable DNA polymerase having 3'-5' exonuclease activity, comprising SEQ ID NO: 2, wherein the histidine in the DIETLYH sequence at position 141 to 147 of SEQ ID NO: 2, has been replaced with another amino acid., does not reasonably provide enablement for **any** modified thermostable DNA polymerase having 3'-5' exonuclease activity, wherein in the $DX_1EX_2X_3X_4H$ sequence within the EXO I region of the thermostable DNA polymerase, histidine (H) has been replaced by another amino acid. The specification does not enable any person skilled in the art to which it pertains, or with which it is most

nearly connected, to make and use the invention commensurate in scope with these claims.

The rejection was stated in the previous office action as it applied to previous claims 1-3, 25-28 and 30. Claims 4-12 have been added to the rejection based on the above 112 second paragraph rejection. Applicants have amended claims 1, 4 and 5 and traverse the rejection as it applies to these newly amended claims. Claims 32-38 are included in this rejection for the same reasons previously stated for claims 1-3, 25-28 and 30.

Applicants traverse this rejection in combination with the above rejection based on a lack of written description on the basis that it is known that the exonuclease I region of the thermostable DNA polymerase is highly conserved and embodiments of the present invention are directed to specific DNA polymerases having the $DX_1EX_2X_3X_4H$ sequence. Applicants further submit that the replacement of histidine (H) by another amino acid, especially aspartic acid, glutamic acid, tyrosine, alanine lysine and arginine, results in the claimed modified thermostable DNA polymerase with: (i) significantly reduced 3'-5' exonuclease activity; (ii) improved amplifying efficiency; or (iii) significantly improved 3'-5' exonuclease activity and/or fidelity on a DNA replication or amplification.

As above, applicants argument is not found persuasive because applicants have not provided a sufficient number of representative species having the $DX_1EX_2X_3X_4H$ sequence encompassed by these claims or guidance as to where these polymerases may be found or the effect of specific mutations beyond merely affecting exonuclease

activity. There is no disclosure of any particular structure to function/activity relationship in the disclosed species, as is further elaborated by applicants argument that some of the claimed modified thermostable DNA polymerases have a reduced 3'-5' exonuclease acvtivity while others have an increased 3'-5' exonuclease activity. The specification also fails to describe additional representative species of these modified thermostable polymerases by any identifying structural characteristics or properties other than the minor structural limitation and activities recited in claims 1-3. Given this lack of additional representative species as encompassed by the claims, Applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise, and exact terms that a skilled artisan would recognize Applicants were in possession of the claimed invention.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any number of amino acid modifications of any thermostable polymerase in the specified $DX_1EX_2X_3X_4H$ sequence. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). It is noted that claims 4-12 have been **included** in this rejection based on the above discussed (See

112 2nd paragraph rejection) interpretation of physicochemical property (3) of claims 4 and 5.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

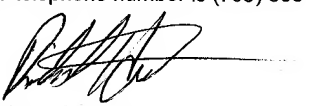
A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Richard G Hutson whose telephone number is (703) 308-0066. The examiner can normally be reached on 7:30 am to 4:00 pm, M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on (703) 308-3804. The fax

phone number for the organization where this application or proceeding is assigned is (703) 305-3014.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.



Richard G Hutson, Ph.D.
Primary Examiner
Art Unit 1652

rgh
1/6/2003